AMENDMENTS TO THE DRAWINGS

The attached sheet of drawings includes changes to Fig. 1. This sheet replaces the original sheet including Fig. 1.

In Fig. 1 the text describing the drawing has been removed.

Attachments: Replacement Sheet

Annotated Sheet Showing Changes

REMARKS

After entry of the amendment, claims 1-11 are pending. Claim 7 has been amended to remove the trademark and further describe the copolymer. Claim 7 has been amended without prejudice and disclaimer and finds support *inter alia* in the original claims and in the specification at page 10, lines 38-41. No new matter has been added.

The specification has been amended to correct the format of the trademark PLURONIC F-68. The trademark has been capitalized and accompanied by the generic terminology "nonionic block copolymer". This amendment finds support in the specification at page 2, lines 11-14. The brief description of figure 1 was amended to incorporate text from the original figure 1. This amendment finds support in the original figure 1. No new matter has been added.

Objections to the Drawings

The objection to Figure 1 as containing text is believed to be rendered moot with the amendments to the description of the drawings and the amended drawing submitted herewith. Withdrawal of the objection is requested.

Objection to the Specification

The specification is amended to conform to the Examiner's request for identification of the PLURONIC trademark for nonionic block copolymers. Withdrawal of the objection is requested.

Claim Rejection under 35 USC 112

Claim 7 is amended to remove the trademark PLURONIC. Withdrawal of the rejection is requested.

Claim Rejections under 35 USC 103

Claims 1-11 are rejected as obvious over Rancke-Madsen et al. (US 6,087,148) in view of Koch et al. (US 6,143,331) and Schulz et al., "Influence of Pluronic F-68 on the Ultrafiltration

of Cell Culture Supernatants," in Carrondo et al. (eds.), Animal Cell Technology, From Vaccines to Genetic Medicine, 1997, Kluwer Academic Publishers. Applicants respectfully traverse.

Rancke-Madsen et al. describes a process and findings very different from the present invention. A process for crystallization of cellulases from microbial fermentation broth, such as *Aspergillus* fermentation broth, is described. Rancke-Madsen et al. teaches the addition of simple organic solvents, such as ethanol and other alcohols and ketones, to crystallize cellulases in microbial fermentation broth.

This alcohol or ketone addition apparently can be done directly, or after concentration of the broth by ultrafiltration. The Patent Office refers to example 1, in which *Aspergillus* broth is concentrated and diafiltered against 2 volumes of water to remove low molecular weight components, such as salt. The resulting solution has a pH of 6.7 and *low conductivity of only 0.7mS/cm* after the diafiltration. Ethanol is then added to induce crystallization and hence purification of the product of interest.

In the Rancke-Madsen et al. article, crystallization of the microbial cellulase is ***induced*** by adding organic solvents at low conductivity (0.7mS/cm) directly OR after adjustment of such conditions by an ultrafiltration/diafiltration process.

In contrast, the present inventors discovered that adjustment of conductivity to a range including that used in Rancke-Madsen et al. is useful ***to prevent or substantially reverse precipitation of solution components*** induced by an organic polymer. Thus, whereas Rancke-Madsen et al. is desirous of inducing protein precipitation and does so by starting at a conductivity of 0.7mS/cm, the presently claimed method aims to prevent or substantially reverse protein precipitation by adjusting conductivity. Claim 3 recites that conductivity is adjusted to below about 6 mS/cm and claim 4 recites that conductivity is adjusted to 0.5-5mS/cm. Both of these ranges encompass the 0.7mS/cm conductivity of the Rancke-Madsen et al. solution. Yet applicants then take the adjusted solution, and subject the retentate to ultrafiltration to further concentrate the macromolecule in solution. In contrast, Rancke-Madsen et al. take the low conductivity solution and precipitate a macromolecule.

If a proposed modification would render the prior art teaching being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification. *In re Gordon*, 733 F.2d 900, 221 USPQ 1125 (Fed. Cir. 1984); *see also*

MPEP 2143.01(V). Here, the purpose of Rancke-Madsen et al. is crystallization of protein. To modify it to obtain the present inventors' goal of preventing precipitation would be contrary to its purpose and the skilled person would find no suggestion to do so.

Furthermore, as the Examiner admits, Rancke-Madsen et al. fails to teach either step (3) of the present invention, namely, a further ultrafiltration after the conductivity has been adjusted, or the use of Pluronic F-68 as a co-concentrating organic polymer.

The Patent Office relies on Koch et al. to supplement the teachings of Rancke-Madsen et al. Yet Koch et al. describes a very different process from the present invention. Koch et al. describes a process in which homogenized tissue is passed through a 30kD ultrafilter, after which the ***filtrate*** (here the product of interest) is repeatedly diafiltered on a second ultrafilter with a lower molecular weight cut-off (3kD).

In contrast, the present invention teaches a process involving at least two ultrafiltration steps interrupted by an adjustment of conductivity with the product being in the ***retentate***.

Applicants found that organic polymers such as Pluronic F-68 also were co-concentrated with the desired macromolecule in the ***retentate***, thereby inducing protein precipitation unless conductivity was adjusted, such as to below about 6 mS/cm.

Koch et al. does not suggest this co-concentration of organic polymers and macromolecule (such as protein) of interest. Instead, Koch et al. teaches use of a diafiltration in which "analogously to a dialysis, undesired components are washed out by multiple filtration with the filtrate solution through the filter." Col. 2, lines 36-42. Thus, Koch et al. suggests using dialysis to remove undesired components, which is contrary to what the present inventors discovered occurs with diafiltration of solutions containing organic polymers such as Pluronic F-68 and macromolecules, such as protein drugs.

Koch et al., like Rancke-Madsen et al., fails to teach Pluronic F-68.

The Patent Office also cites Schulz et al. as suggesting the desirability of ultrafiltration and the dependence of ultrafiltration on solute-membrane interactions. Schulz et al. simply

teaches that Pluronic can be in principle completely removed through repeated diafiltration, i.e. passed into the filtrate, using large molecular weight cut-off membranes.

In contrast, the present inventors have found that Pluronic practically completely co-concentrates with the protein of interest, and hence remains in the retentate, under practically relevant conditions and with molecular weight cut-offs required for concentrating protein drugs. The present inventors have further found that this co-concentration can induce protein precipitation and discovered a method to prevent such Pluronic-induced protein precipitation. The claimed method of solving the problem is not suggested by Schulz et al.

The Examiner states that the claims would have been obvious because a person of ordinary skill has "good reasons to pursue the known options within his or her technical grasp," and these options "lead[s] to the anticipated success." Office Action, p. 7. Yet there is no teaching cited that adjustment of conductivity is a "known option" when membrane fouling with organic polymers occurs.

Furthermore, success cannot be anticipated because the references teach process elements for different purposes. As stated above, Rancke-Madsen et al. teaches a process to crystallize protein. Koch et al. is focused on extraction of a thymus extract to retain its biological activity and stability during storage. Each of these purposes is distinct. The skilled person would not anticipate success by picking elements from these two distinct processes and combining them.

Furthermore, this alleged motivation based on "common knowledge and common sense" is completely devoid of any reference to a technical ground specific to the present invention. As such, the Patent Office has failed to make a prima facie case of obviousness. "[R]ejections on obviousness cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." *KSR International Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 1741 (2007), quoting *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006). A statement that modifications of the prior art to meet the claimed invention would have been "well within the ordinary skill of the art at the time the claimed invention was made" because the references relied upon teach that all aspects of the claimed invention were individually known in the art is not sufficient to establish a *prima facie*

case of obviousness without some objective reason to combine the teachings of the references. *Ex parte Levengood*, 28 USPQ2d 1300 (Bd. Pat. App. & Inter. 1993); *see also* MPEP § 2143.01 IV. The Examiner has not provided any explanation, rationale, or suggestion in the references cited for why it would be obvious to substitute the methods. Such a statement lacks the specificity required to support a legal conclusion of obviousness and is thus insufficient to establish *prima facie* obviousness.

Conclusion

In view of the above amendments and remarks, Applicants urge that the claims are in condition for allowance. A petition for extension of time with the requisite fee are submitted herewith electronically.

Applicants believe no additional fee is due with this response. However, if a fee is due, please charge our Deposit Account No. 03-2775, under Order No. 07430-00191-MSB-8012US from which the undersigned is authorized to draw.

Dated:

Respectfully submitted,

Electronic signature: /Christine M. Hansen/
Christine M. Hansen
Registration No.: 40,634
CONNOLLY BOVE LODGE & HUTZ LLP
1007 North Orange Street
P. O. Box 2207
Wilmington, Delaware 19899-2207
(302) 658-9141
Attorney for Applicant